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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,765	01/29/2002	Nobuyuki Itoh	201130.408D1	9697

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 05/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/060,765	ITOH ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-18 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-18 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/29/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Sequence alignment; Notice to comply with requirements for patent application containing nucleotide sequence and/or amino acid sequence disclosure.

DETAILED ACTION

Election/Restrictions

1. Applicants' election of Group II, claims 12-18 and 22, on February 2, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicants' preliminary amendment filed on January 29, 2002 has been entered. Claims 1-11, 19-21, and 23-59 have been canceled. Claims 12-18 and 22 are pending and under consideration.

Sequence Compliance

3. The amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 because the amino acid sequences shown at page 10 (lines 12 and 18) fail to be identified with a sequence identifier. An amendment directing its entry into the specification must be provided. It is suggested that the amino acid sequence of line 12 of page 10 be identified by SEQ ID NO: 11, whereas the amino acid sequence of line 18 of page 10 be identified by SEQ ID NO: 13, as listed in the Sequence Listing. Please see attached Notice to Comply with Requirements for Patent Application Containing Nucleotide Sequence and/or Amino acid Sequence Disclosure.

Information Disclosure Statement

4. The information disclosure statement filed on January 29, 2002 has been considered by the Examiner and a signed copy of form PTO-1449 is attached to the office action.

Drawings

5. The drawings filed on May 21, 2002 are accepted by the Examiner.

Objection to the Disclosure

6. The disclosure is objected to because of the following informalities: the brief description of drawings fails to refer to panels A and B of Fig. 4, 5, and 7-9. Appropriate correction is required.

Abstract

7. The abstract of the disclosure is objected to because of the presence of typed materials, which are not related to the disclosure. Correction is required. See MPEP § 608.01(b).

Claim Rejections—35 USC § 112, 1st paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 12-16 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4 and its epitope-bearing portion of SEQ ID NO: 4 comprising SEQ ID NO: 7 or 8, does not reasonably provide enablement for (i) a genus of polypeptides comprising a fragment of SEQ ID NO: 4, a variant or homologue of SEQ ID NO: 4 or its fragment; and (ii) an epitope-bearing portion of SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The breadth of the claims. The claims are drawn to a genus of polypeptides comprising SEQ ID NO: 4, a fragment of SEQ ID NO: 4, and a variant or homologue of SEQ ID NO: 4/its fragment with either 95% sequence identity to SEQ ID NO: 4/its fragment or at least one conservative amino acid substitution. Claim 15 is drawn to an epitope-bearing portion of the polypeptide of SEQ ID NO: 4, whereas claim 15 is drawn to an epitope-bearing portion of SEQ ID NO: 4 comprising between 10 and 50

contiguous amino acids of SEQ ID NO: 4. Thus, the claims are remarkably broad and encompass an enormous genus of fragments, variants and homologues of SEQ ID NO: 4, without recitation of any specific functional limitation or particular conserved structure.

Nature of the invention and the state of the prior art. The present invention is related to the polypeptide of SEQ ID NO: 4, which belongs to the fibroblast growth factor (FGF) family. Numerous FGFs are known in the art, including the FGF polypeptide taught by Agarwal et al. (US20010012628A1, Publication Date: August 9, 2001; earliest priority date: November 5, 1999), which is shares 99.4% amino acid sequence identity with SEQ ID NO: 4. The biological functions or properties of members of the fibroblast growth factor family are very divergent. For example, FGF-1 and FGF-2 are potent mitogens for a variety of cell types; the gene encoding FGF-3 is a common target for activation by the mouse mammary tumor virus whereas the genes encoding FGF-4, FGF-5, and FGF-6 have transforming activity when introduced into NIH 3T3 cells. FGF-7, FGF-8, and FGF-9 are mitogens for ketatinocytes, mammary carcinoma cells, and astrocytes, respectively (Smallwood et al, *Proc. Natl. Acad. Sci. USA* 93:9850-9857, 1996. See page 9850, 1st paragraph of left column). Despite the fact that numerous FGFs were discovered, as noted above, there were no sufficient teachings on how to make and/or use the majority of the species encompassed in the claimed genus. It is routine for an artisan to produce an antibody with an epitope of a polypeptide. However, such an antibody may also bind to a homologue of the polypeptide or even an entirely different polypeptide.

The amount of direction or guidance presented and the existence of working examples. Despite the fact that the instant disclosure provides sufficient guidance on how to make and use the polypeptide set forth in SEQ ID NO: 4 and its two epitope-bearing fragments of SEQ ID NO: 7 and 8, the instant disclosure fails to provide sufficient guidance/direction or working examples on the structural and functional requirements commensurate in scope with what is encompassed by the instant claims since the general disclosure that one could make and use SEQ ID NO: 4 could not be used to be such guidance as to guide one skilled in the art to make and use a variant, homologue or a fragment of SEQ ID NO: 4. The specification is silent with respect to which residues may be altered without loss of activity. The disclosure does not show (i) which portions of the polypeptide of SEQ ID NO: 4 are critical to its activity; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO: 4 will result in a mutant or a fragment with the same functions as that of the polypeptide set forth in SEQ ID NO:4. Thus, the specification fails to provide sufficient direction or working example on how to make those variants, homologues and fragments that have the same function as that of the polypeptide of SEQ ID NO: 4 or how to use those variants, fragments and homologues that do not have the same functional activity as that of the polypeptide of SEQ ID NO: 4.

Furthermore, while the specification discloses fragments of the polypeptide of SEQ ID NO: 4 can be used for preparing an antibody, such an antibody does not necessarily bind to the full length polypeptide of SEQ ID NO: 4; and there is no

requirement in the claims that the antibody produced by an epitope-bearing fragment bind the polypeptide of SEQ ID NO: 4.

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary. Although one skilled in the art certainly has the technology and skills to make and use any polypeptides with a defined amino acid sequence and a defined biological activity, it is unpredictable whether a variant, homologue, or a fragment of SEQ ID NO: 4 would retain the same function as that of the full length of polypeptide of SEQ ID NO: 4 . The state of the art (See, e.g., Ngo, et al, *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz, et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495) is such that the relationship between sequence of a protein and its activity is not well understood and is not predictable. Excising out portions of a protein or modifications to a protein, e.g., by substitutions or deletions, would often result in deleterious effects to the overall activity and effectiveness of the protein. Furthermore, while an artisan can make an antibody using an polypeptide, it is unpredictable whether an antibody produced using an epitope-bearing portion of SEQ ID NO: 4 other than SEQ ID NO: 7 and 8 binds to the full length of SEQ ID NO: 4. Thus, it would take undue experimentation for one skilled in the art to make and/or use the claimed genus of polypeptides.

Accordingly, while being enabling for an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4 and its epitope-bearing portion of SEQ ID NO: 4 comprising SEQ ID NO: 7 or 8, the specification does not reasonably provide

enablement for the genus of variants and fragments of the polypeptide of SEQ ID NO: 4 encompassed by the instant claims. Thus, it would require undue experimentation for one skilled in the art to make and/or use the claimed invention commensurate in scope with the claims.

10. Claims 12-16 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 12-14 and 22 are drawn to a genus of polypeptides comprising SEQ ID NO: 4, a fragment of SEQ ID NO: 4, and a variant or homologue of SEQ ID NO: 4/its fragment with either 95% sequence identity to SEQ ID NO: 4/its fragment or at least one conservative amino acid substitution. Claim 15 is drawn to an epitope-bearing portion of the polypeptide of SEQ ID NO: 4, whereas claim 15 is drawn to an epitope-bearing portion of SEQ ID NO: 4 comprising between 10 and 50 contiguous amino acids of SEQ ID NO: 4. The claim does not require that the polypeptide or an epitope-bearing portion of the polypeptide of SEQ ID NO: 4 possess any biological

activity, nor any particular conserved structure, or other disclosed distinguishing feature.

The instant disclosure of two FGF polypeptides, human FGF polypeptide of SEQ ID NO: 4 and mouse FGF polypeptide of SEQ ID NO: 2, and their encoding nucleic acids, as well as two epitope fragments consisting of 15 and 16 contiguous amino acids of SEQ ID NO: 4, does not adequately support the scope of the claimed genus. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of the polypeptides, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. However, the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of polypeptide. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Other than SEQ ID NOS: 7 and 8, there is no sufficient description on the epitope-bearing portion of SEQ ID NO: 4. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed polypeptide as being identical to those instantly claimed.

Due to the breadth of the claim genus and lack of sufficient recitation of distinguishing identifying characteristics, one skilled in the art would not recognize

from the disclosure that the applicant was in possession of the claimed genus. Therefore, only isolated polypeptide comprising SEQ ID NO: 4 and its epitope-bearing portion of SEQ ID NO: 4 comprising SEQ ID NO: 7 or 8, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections—35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 12-14 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Agarwal et al. (US20010012628A1, Publication Date: August 9, 2001; earliest priority date: November 5, 1999).

Agarwal et al. teach an FGF-19a polypeptide, which is 99.4% amino acid sequence identity with SEQ ID NO: 4. The FGF-19a polypeptide only differs from SEQ ID NO: 4 at position 174 (see attached sequence alignment) and comprises amino acids from about 1 to about 177 of SEQ ID NO: 4. Since the FGF-19a polypeptide has FGF activity, the substitution of amino acid residue "L" with "P" in the SEQ ID NO: 4 is considered a conservative amino acid substitution. Agarwal et al.

further teach a composition, a vaccine formulation, comprising an FGF-19a polypeptide and a suitable carrier (top of left column of page 6). Thus, the reference of Agarwal et al. meets the limitations of claims 12-14 and 22.

Conclusion

13. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (571) 272-0887.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [Gary.Kunz@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published

in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Ruixiang Li

Ruixiang Li, Ph.D.
Examiner
May 20, 2004

Application No.: 10/060,765

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: the amino acid sequences shown at page 10 (lines 12 and 18) fail to be identified with a sequence identifier.

Applicant Must Provide:

- [ ] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An amendment directing its entry into the specification must be provided. It is suggested that the amino acid sequence of line 12 of page 10 be identified by SEQ ID NO: 11, whereas the amino acid sequence of line 18 of page 10 be identified by SEQ ID NO: 13, as listed in the Sequence Listing.
- [ ] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
For CRF Submission Help, call (571) 272-2510
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Technical Assistance..... (571) 272-2510

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